Reactogenicity of fluid compared with adsorbed diphtheria–pertussis–tetanus vaccine

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Shortly after the introduction of adsorbed diphtheria–pertussis–tetanus (DPT) vaccine in British Columbia the frequency of reports of reactions to the vaccine increased. As the reasons for the increase were not clear a study was carried out in five health units to compare the reactions to adsorbed DPT vaccine manufactured by Wyeth Ltd. and Connaught Laboratories Ltd. and fluid DPT vaccines manufactured by Connaught, all the vaccines being injected in the anterolateral thigh. From the responses on 1619 questionnaires that the parents of vaccinated children had completed it was found that the relative risk of a reaction was higher with the fluid than with the adsorbed Connaught vaccine (1.7 for redness and 1.8 for swelling on the day of vaccination but 1.0 for drowsiness and 1.3 for persistent crying). The size and duration of local redness and swelling were also greater with the fluid than with the adsorbed Connaught vaccines. The results with the Wyeth and Connaught vaccine were very similar. Only 10% of the parents said that there had been no reaction; 9% said that the reaction was severe, and 6% said that it was completely unacceptable. The overall frequency of local reactions was 86.1%.

Quand on a commencé à utiliser en Colombie-britannique les triples vaccins diphtérie–coqueluche–tétanos (DCT) sous leur forme adsorbée, on a noté peu après une augmentation du nombre de rapports de réactions adverses. Afin d'examiner les causes de cette augmentation il est institué une enquête comparative dans cinq unités sanitaires auprès des parents au moyen d'un questionnaire. Les 1619 réponses montrent, au fait, que la fréquence relative des réactions adverses au vaccin non-adsorbé Connaught est plus grande que pour son produit adsorbé, soit un factuer de 1,7 pour la rougeur et de 1,8 pour l'oedème le jour de l'injection, celle-ci ayant été faite à la région antéro-externe de la cuisse dans tous les cas. L'étendue et la durée moyennes de ces altérations locales sont aussi plus grandes dans le cas du vaccin non-adsorbé. Quant aux symptômes généraux, les facteurs correspondants sont 1,0 pour la somnolence et 1,3 pour les pleurs prolongés. Les observations concernant le produit adsorbé Wyeth sont fort semblables. Dans l'ensemble, seuls 10% des parents ne rapportent aucune réaction; dans 9% des cas la réaction est grave, et dans 6% des cas on la juge même "inacceptable". La fréquence globale des réactions locales est de 86,1%.

In Canada before 1981 a fluid DPT (diphtheria–pertussis–tetanus) preparation was used for routine immunization in children. At the recommendation of the National Advisory Committee on Immunization[1] and others[2-4] adsorbed vaccines, which produced superior antibody responses with a reduced volume of vaccine, were introduced in 1981. Diphtheria and tetanus toxoids were adsorbed to aluminum phosphate, and then pertussis vaccine was added. The benefits of using adsorbed DPT vaccine have recently been reviewed.[5]

In British Columbia it became apparent that the use of adsorbed DPT vaccine, manufactured by Connaught Laboratories Ltd., Willowdale, Ont., was temporally associated with a marked increase in the frequency of reports of reactions, mainly local, to the vaccine.[6-8] Possible explanations for the increase include greater reactogenicity of the adsorbed vaccine compared with the Connaught fluid vaccine, the change in site of inoculation to the anterolateral thigh,[9] the use of intramuscular rather than subcutaneous administration of fluid DPT vaccine, increased awareness of reactions by public health nurses (a reporting artefact) or some undetermined reason.

The first explanation seemed the most likely, but it was also possible that all adsorbed vaccines might be more reactogenic than fluid vaccines. Therefore, a clinical trial was undertaken to determine whether the Connaught adsorbed DPT vaccine was more reactogenic than the Connaught fluid vaccine and whether the former was more reactogenic than the adsorbed vaccine manufactured by Wyeth Ltd., Philadelphia, Pennsylvania that was used in the United States.

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Methods

In area 1, which included the West Kootenay and Selkirk health units, Wyeth adsorbed DPT vaccine (lot 71401) was compared with Connaught adsorbed DPT vaccine (lot 305-12 or 308-11), and in area 2, which included the Cariboo, Northern Interior and Peace River health units, Connaught fluid DPT vaccine (lot 1404-11) was compared with Connaught adsorbed DPT vaccine (lot 305-12 or 308-11). In these health units vaccination is carried out only in public clinics.

Parental consent was received for all the children in the study. The parents were advised that the children would receive one of two equivalent vaccines. The children were assigned vaccine at the registration area, 10 children receiving one vaccine and the next 10 receiving the other. The parents did not know which vaccine had been given, but the clinic staff and nurses did. So that site would not be a variable, all the vaccines were given in the anterolateral thigh. Adsorbed vaccine, 0.5 mL, was administered intramuscularly, and fluid vaccine, 1.0 mL, was administered subcutaneously, in accord with the manufacturers' directions. All the children were given trivalent polio vaccine orally in addition to DPT vaccine. The vaccination schedule recommended that the children receive the DPT and polio vaccines initially at 2, 4 and 6 months of age, with a booster of each at 18 months of age at the immunization clinics.

The parents were asked to answer a questionnaire on reactions to the vaccine and to return it to the immunization clinic. The questionnaire asked about local reactions (redness, swelling, pain and refusal to move the leg at 24 and 48 hours after vaccination) and systemic reactions (fever, drowsiness, persistent crying and others); estimates of the size and duration of redness and swelling and of the duration of crying were requested. The parents were also asked to rate the reactions as none, mild, moderate or severe and to score their "acceptability" from 1 (completely acceptable) to 5 (completely unacceptable). The questionnaires were coded centrally and the data processed by the department of health care and epidemiology, University of British Columbia.

Results

A total of 2176 children were eligible for the study. However, in 184 instances (8%) parental consent was refused. For the remaining 1992 children 1619 questionnaires were returned, for a response rate of 81%. In area

Table I—Number of doses of diphtheria–pertussis–tetanus (DPT) vaccine according to vaccination schedule

Geographic area; type of DPT vaccine	Order of vaccination; no. (and %) of doses				Total no. of doses
	First	Second	Third	Fourth	
1					
Wyeth adsorbed	109 (27)	124 (31)	89 (22)	80 (20)	402
Connaught adsorbed	84 (33)	70 (27)	56 (22)	47 (18)	257
2					
Connaught fluid	143 (30)	124 (26)	98 (21)	105 (22)	470
Connaught adsorbed	147 (30)	130 (26)	112 (23)	101 (21)	490
Total	483	488	355	333	1619

Table II—Frequency of local and systemic reactions to adsorbed and fluid DPT vaccines

Reaction	Vaccine; no of children with reported reactions/total no. of children vaccinated (and % with reactions)				Relative risk of reactions with fluid/adsorbed vaccine	p value*
	Area 1		Area 2			
	Wyeth adsorbed	Connaught adsorbed	Connaught fluid	Connaught adsorbed		
Redness						
Day of injection	194/394 (49)	132/249 (53)	360/457 (79)	227/482 (47)	1.7	< 0.001
Day after injection	132/385 (34)	88/247 (36)	255/480 (53)	134/470 (28)	1.9	< 0.001
Swelling						
Day of injection	166/391 (42)	104/252 (41)	317/464 (68)	181/480 (38)	1.8	< 0.001
Day after injection	119/382 (31)	62/244 (25)	231/452 (51)	116/468 (25)	2.1	< 0.001
Refusal to move leg	114/391 (29)	65/251 (26)	146/458 (32)	146/477 (31)	1.0	NS
Fever						
Day of injection	143/389 (37)	84/253 (33)	209/461 (45)	179/484 (37)	1.2	< 0.02
Day after injection	87/365 (24)	55/252 (22)	98/447 (22)	99/458 (22)	1.0	NS
Drowsiness	156/363 (43)	100/241 (41)	192/435 (44)	200/448 (45)	1.0	NS
Persistent crying	188/383 (49)	114/246 (46)	235/457 (51)	191/471 (40)	1.3	< 0.01

*NS = not significant.

1, 402 questionnaires were returned for the children given Wyeth adsorbed DPT vaccine and 257 for those given Connaught adsorbed DPT vaccine, and in area 2 470 questionnaires were returned for the children given Connaught fluid DPT vaccine and 490 for those given Connaught adsorbed DPT vaccine. The response rate was 80% in area 1 and 77% in area 2. As not all the questionnaires were complete, the totals in the tables vary somewhat.

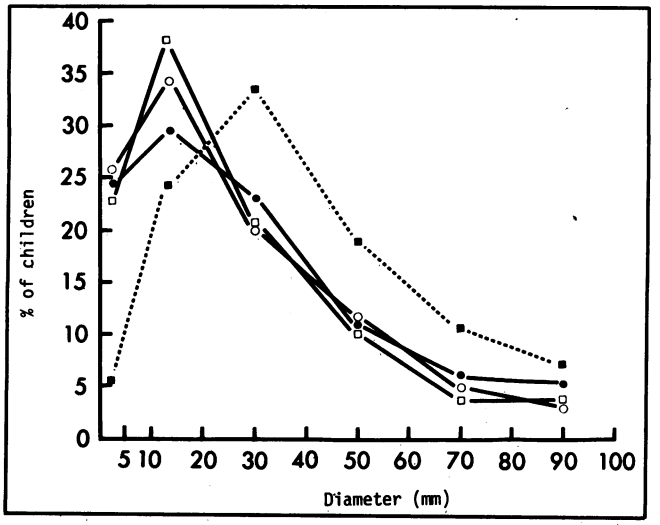

Fig. 1—Size of red area in children from area 1 receiving Wyeth adsorbed DPT (diphtheria–pertussis–tetanus) vaccine (● — ●) or Connaught adsorbed vaccine (○ — ○) and in those from area 2 receiving Connaught adsorbed vaccine (□ — □) or Connaught fluid vaccine (■ — ■).

The sex and age distribution of the children was similar in the four groups. The numbers of doses of vaccine given to each group at each point in the vaccination schedule were also similar (Table I).

Among the children in area 1 there was no difference in the frequency of reactions caused by the two adsorbed vaccines (Table II). However, among those in area 2 the fluid vaccine was more reactogenic than the adsorbed vaccine, significantly more often causing local redness or swelling, fever on the day of the injection or persistent crying. No differences were noted in the frequency of refusal to move the leg or of drowsiness. The frequency of reactions caused by the adsorbed vaccines in areas 1 and 2 was similar. The fluid vaccine produced larger and more persistent areas of redness (Fig. 1) and swelling than the adsorbed vaccines. However, there was no difference in the duration of crying caused by either vaccine.

According to the parents' ratings of the severity of the reactions the fluid vaccine produced more "moderate" reactions than the adsorbed vaccines; however, the frequency of severe reactions was similar with all the vaccines (Table III). The parents also felt that the fluid vaccine produced less acceptable reactions than the adsorbed vaccines (Table IV). The number of signs and symptoms reported was greater with the fluid vaccine than with the adsorbed vaccine.

Discussion

The enrolment of children in the comparative trial of the Wyeth and Connaught adsorbed DPT vaccines in

Table III—Parents' ratings of the severity of the reactions

Geographic area; type of DPT vaccine	Severity of reaction; no. (and %) of ratings				Total no. of ratings
	None	Mild	Moderate	Severe	
1					
Wyeth adsorbed	41 (11)	197 (51)	108 (28)	40 (10)	386
Connaught adsorbed	26 (10)	139 (56)	64 (26)	19 (8)	248
2					
Connaught fluid	34 (8)	170 (38)	202 (44)	47 (10)	453
Connaught adsorbed	58 (12)	237 (50)	144 (31)	32 (7)	471
Total	159 (10)	743 (48)	518 (33)	138 (9)	1558

Table IV—Parents' scores on the "acceptability" of the reactions

Geographic area; type of DPT vaccine	Acceptability;* no. (and %) of scores					Total no. of scores
	1	2	3	4	5	
1						
Wyeth adsorbed	205 (52)	67 (17)	53 (13)	43 (11)	27 (7)	395
Connaught adsorbed	132 (52)	51 (20)	38 (15)	19 (8)	13 (5)	253
2						
Connaught fluid	190 (41)	95 (21)	102 (22)	43 (9)	31 (7)	461
Connaught adsorbed	259 (54)	97 (20)	77 (16)	27 (6)	18 (4)	478
Total	786 (50)	310 (20)	270 (17)	132 (8)	89 (6)	1587

*Scored from 1 (completely acceptable) to 5 (completely unacceptable).

area 1 was not done according to protocol: equal numbers of children were not enrolled in each group. However, the distribution of doses was similar in these two groups, and the frequency of reactions was similar in these two groups and in the group in area 2 that received adsorbed vaccine. The lack of a difference with an independent sample indicates that a systematic bias was not present and that the results showing that the Wyeth and Connaught adsorbed DPT vaccines produced reactions at the same rates were reliable.

The rate of refusal to participate in the study was low (8%). Most parents refused because they did not want to fill out a questionnaire. The response rates were similar for the parents from both study areas. Although no data are available on this point, the parents whose children had a reaction to the vaccine may have been more likely to return the questionnaire. However, if this trend existed it should not have biased the comparison of the frequency of reactions since the parents did not know which vaccine each child had received. It could have resulted in an overestimate of the frequency of reactions.

The variation between the tables in the total number of responses for a particular vaccine reflects both incompleteness of some of the questionnaires and errors in data coding. When the parents did not give a response the child was not included in the denominator. Hence, the denominators for most of the questions were different. In some instances the lack of a response about a particular type of reaction may indicate that no such reaction occurred; thus, the calculated frequency of that reaction would be falsely increased. The reactions for which the number of parents responding was low cannot, therefore, be properly evaluated except in a comparative sense.

The hypothesis tested in both geographic areas was that the frequency of reactions to the vaccines was not the same and could differ in either direction (two-tailed hypothesis). From the results of the manufacturers' field trials[3] and of earlier experience with adsorbed vaccine[6-8] it was expected that the fluid vaccine would be less reactogenic than the adsorbed vaccines; however, the fluid vaccine produced more local reactions, and these reactions affected larger areas and lasted longer than those produced by the adsorbed vaccines. This may be because parents are more likely to report reactions than are study personnel who are looking for serious or complicated reactions.

Two recent studies of reactions to adsorbed vaccines showed that these vaccines are highly reactogenic (Table V).[10,11] Those investigators also gave questionnaires to the parents. Differences between their questionnaires and the one used in this study may account for the higher frequency of local reactions, particularly redness, reported by the parents in our study. The lack of a thermometer in most of the households in our study may account for the lower frequency of fever in this study. The presence of fever was most often determined by the parent's subjective impression rather than by a numerical value even though the use of "fever strips" or thermometers was encouraged.

Murphy and colleagues[12] found that a severe local reaction, defined as a swollen area more than 10 mm in diameter, was present in 8.3% of their study sample. In my study the rates at which vaccination caused redness or swelling of an area more than 20 mm in diameter were 31.2% and 26.7% respectively.

In the present study the parents were asked to estimate the severity of the reactions. Overall, 9% of the parents rated the reactions as severe, and 6% rated them as completely unacceptable. Only 10% said that no reaction had occurred, but 50% said the reactions had been completely acceptable and 20% that they had been acceptable.

Nevertheless, DPT vaccine, whether adsorbed or fluid, produces local reactions in a high proportion of children. One study found that fewer reactions occurred when the injection was given in the buttock.[13] However, this site is not recommended for routine vaccination.[9]

It is clear from this study that the switch in British Columbia to an adsorbed DPT vaccine from a fluid DPT vaccine, while greatly increasing the frequency of reports of reactions, was not due to the different route of injection or to greater reactogenicity of the adsorbed vaccine. The use of a particular manufacturer's products did not seem to be responsible, as the results with the Wyeth and Connaught adsorbed vaccines were very similar, although differences between lots in the frequency of reactions have been noted in other studies.[13,14] Whether the increase in the frequency of reactions could have been due to increased concern caused by the use of a new vaccine, to the different site of injection or to a combination of these and other factors was not assessed in this study. Although substantial numbers of children were observed, severe systemic reactions were not reported. As the frequency of severe systemic reactions is generally low, perhaps 1/100 000,[15] or even lower,[16,17] this finding is not unexpected.

Wilson[16] defined a simple reaction as "one that is experienced in greater or less degree by the majority of persons receiving the vaccine, is attended by local and constitutional disturbance lasting not more than a few

Table V—Comparison of results of recent studies of reactions to adsorbed DPT vaccines

Reaction	Study (and no. of questionnaires returned); % of children with reported reactions		
	Cody et al[10] (15 752)	Barkin et al[11] (1232)	Present study* (1619)
None		7.0	10.2
Local		72.2	86.1
Mild		23.2	47.6
Moderate		58.6	33.2
Severe		7.1	8.8
Fever		53.6	38.7
Temperature greater than 38.9°C	6.1	4.2	NR
Persistent crying	3.1	12.9	44.8
Redness	35.4		49.2
Swelling	38.3		53.3
Pain	45.7		54.5

*NR = not recorded.

days and causes no local destruction of tissue or general manifestation other than those common to a febrile illness". The present study indicates that while such reactions may be "simple", they are not acceptable to many parents. The high frequency of the reactions and the parents' anxiety about them indicate that the benefits and risks of DPT vaccination need to be kept in mind and that the search for less reactogenic but equally or more effective vaccines needs to be continued.

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